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PRINCIPAL INVESTIGATOR: Maureen Sanderson, Ph.D.

CONTRACTING ORGANIZATION: Meharry Medical College
Nashville, TN 37208

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Maureen Sanderson

E-Mail: msanderson@mmc.edu

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14. ABSTRACT

The purpose of this HBCU/MI Partnership Training Award is to train Meharry Medical College faculty to conduct independent breast cancer research by collaborating with faculty from Vanderbilt University Medical Center. Year 1 was a training year and during Years 2 through 4 a case-control study of obesity, insulin resistance and mammographic breast density is being conducted. Specific aims include: 1) to assess mammographic breast density through digital mammograms; for a sample of women we will also assess mammographic breast density through film mammograms to determine the diagnostic accuracy of digital versus film mammogram, 2) to obtain information on breast cancer risk factors including health literacy, and to collect anthropometric measurements and fasting blood, 3) to assay blood for select hormones and growth factors, 4) to perform statistical analyses to determine the associations between obesity and insulin resistance and mammographic breast density, and 5) to evaluate patients' ability to understand their mammogram findings as they are explained by their medical provider. Drs. Sanderson, O'Hara and Khoder attended/presented at conferences and published a manuscript. Continuing institutional review board approval was obtained for the Mammographic Breast Density Project. Subject recruitment, data collection and processing, auditing quality assurance, and performing interim analyseswere completed on 388women.

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Epidemiology/biostatistics, hormone metabolism

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Introduction

The purpose of this HBCU/MI Partnership Training Award is to train Meharry Medical College (MMC) faculty to conduct independent breast cancer research by collaborating with faculty from Vanderbilt University Medical Center (VUMC). Three MMC faculty will undergo intensive training supervised by three VUMC faculty during year 1 with additional training taking place in subsequent years. To reinforce training, faculty from MMC and VUMC will conduct a case-control study of mammographic breast density to investigate its' association with obesity and insulin resistance in years 2 through 4. Cases (n=150) whose breasts are in the upper quartile of breast density and controls (n=850) whose breast are in the lowest three quartiles of breast density, will be recruited from the MMC Center for Women's Health Research which serves a medically underserved population. Specific aims are: 1) to assess mammographic breast density through digital mammograms; for a sample of women we will also assess mammographic breast density through film mammograms to determine the diagnostic accuracy of digital versus film mammogram, 2) to obtain information on breast cancer risk factors including health literacy, and to collect anthropometric measurements and fasting blood, 3) to assay blood for select hormones and growth factors, 4) to perform statistical analyses to determine the associations between obesity and insulin resistance and mammographic breast density, and 5) to evaluate patients' ability to understand their mammogram findings as they are explained by their medical provider.

Body

As indicated in the Statement of Work (Appendix), this project is occurring in two phases, the training phase (year 1) and the investigation phase (years 2 through 4). We completed all training tasks during the first year of the project; however, ongoing training tasks include the attendance and presentation of MMC investigators at workshops and conferences, the publication of manuscripts utilizing existing data, and Institutional Review Board (IRB) approval of the Mammographic Breast Density Project. Dr. Waseem Khoder an MMC co-investigator began a fellowship in urologic gynecology and was replaced by Dr. Nia Foderingham, a Preventive Medicine physician with a Master's of Science in Public Health, effective October 21, 2013. Dr. Maureen Sanderson attended the American Public Health Association conference, Dr. Heather O'Hara attended the American College of Preventive Medicine conference, and Dr. Khoder attended the American College of Obstetrics and Gynecology conference. Using data from Dr. Sanderson's previous study (DAMD17-03-1-0274), Drs. Sanderson, O'Hara and Khoder presented a poster at the Research Centers in Minority Institutions International Symposium on Health Disparities and published a manuscript (Appendix includes abstract and publication). We obtained continuing IRB approval for the project from MMC on 8/19/2013, VUMC on 3/18/2013, and the Department of Defense (DOD) on 9/9/2013.

During the third year of the project we continued in the investigation phase. The study team has met on a monthly basis and the investigative team (Drs. Sanderson, O'Hara, and Khoder/Foderingham from MMC and Drs. Dupont, Shu and Peterson from VUMC) has met on a quarterly basis. Between October 12, 2012 and October 11, 2013 we completed subject recruitment and data collection of 285 participants for a total of 414 participants of the 480 participants we had proposed (Appendix includes tables of preliminary results). We partially completed investigation tasks 2 through 5 by quantitating mammographic breast density measurement; recruiting subjects and collecting data; assessing health literacy; and processing blood samples, taking body measurements and performing assays. We partially completed

investigation tasks 7 and 8 by conducting ongoing quality assurance audits to ensure patient safety and integrity, and conducting interim analyses.

During the fourth year of the project, we will continue with the investigation phase. Drs. Sanderson, O'Hara and Foderingham will attend workshops and conferences when possible. We will fully complete investigation tasks 2 through 5, and 7 and 8. We will seek a no cost extension to fully complete investigation tasks 6 and 9 in the fifth year of the project.

Key Research Accomplishments

- Completed ongoing training task by Drs. Sanderson, O'Hara and Khoder attending conferences, presenting a poster at a conference, and publishing a manuscript.
- Completed ongoing training task by obtaining continuing IRB approval from three entities.
- Partially completed investigation tasks 2 through 5 by recruiting subjects and collecting and processing data (digital mammograms, blood, body measurements, questionnaires including health literacy).
- Partially completed investigation tasks 7 and 8 by conducting quality assurance audits and interim analyses.

Reportable Outcomes

1) Manuscripts

Sanderson M, Perez A, Weriwoh ML, Alexander LR, Peltz G, Agboto V, O'Hara H, Khoder W. Perinatal factors and breast cancer risk among Hispanics. J Epidemiol Global Health 2013;3:89-94.

2) Abstracts

Sanderson M, Bevel MS, Alexander L, Fair AM, Peltz G, O'Hara, Khoder W. Hormone replacement therapy and breast cancer among Hispanics. 13th RCMI International Symposium on Health Disparities. San Juan, Puerto Rico, December 2012.

3) Grants

Not applicable

Conclusions

The overall goal of this proposed HBCU/MI Partnership Training Award is to strengthen the existing collaborative relationship between the minority institution, MMC, and the collaborating institution, VUMC. The investigators from MMC and VUMC have mutual interests in studying the interplay of lifestyle and molecular factors on breast cancer risk as measured by its precursor, mammographic breast density. High mammographic breast density is comparable in its predictive magnitude of risk to historically well-established breast cancer risk factors. The biological basis for the association between higher percentage of density and risk of

breast cancer is not clear but may be related to increased stroma and glandular tissue in dense breasts through estrogen exposures or production of certain growth factors including insulin-like growth factor-I (IGF-I) or adipokines such as leptin. Very few studies have focused on obesity and insulin resistance as they relate to mammographic breast density. We hypothesize that: 1) obesity and insulin resistance, defined as high levels of C-peptide, will be positively associated with high mammographic breast density, and 2) these associations will be more pronounced among women with high levels of IGF-I and high levels of leptin.

This project will establish associations between some lifestyle and molecular factors and mammographic breast density; known to be linked to subsequent breast cancer, especially in minority and medically underserved women. By identifying biomarkers that influence mammographic breast density in minority women, this project may provide therapeutic targets for new prevention strategies in this population. While faculty from VUMC has expertise in breast cancer research, faculty from MMC has strong ties with minority communities in Nashville and Davidson County. To date, limited breast cancer research has been conducted at MMC. By partnering together, MMC and VUMC hope to build infrastructure to conduct population-based case-control studies of breast cancer at MMC, and to establish an outstanding collaborative breast cancer research program.

References

Sanderson M, Perez A, Weriwoh ML, Alexander LR, Peltz G, Agboto V, O'Hara H, Khoder W. Perinatal factors and breast cancer risk among Hispanics. J Epidemiol Global Health 2013;3:89-94.

Statement of Work

Phase 1: Training Phase (Year 1)

Task 1: (Drs. Sanderson, Khoder, Jones, Richard-Davis, Disher, Sanderson, Dupont, Peterson and Shu) (Jones replaced by O'Hara and Khoder replaced by Foderingham)

1a. Drs. Sanderson, Khoder and Jones audit courses at Summer Research program at University of Michigan (months 6-7).
1b. Dr. Jones begins the Meharry Medical College, Master's of Science in Clinical Investigation Program (months 1-30).
1c. Consult with advisory board and health providers in the Center for Women's Health Research (CWHR) to design a cross-sectional study for measurement of mammographic breast density, related hormones and health literacy (months 1-3).
1d. Develop and finalize study protocol for recruitment of participants (months 1-6).
1e. Develop and finalize study protocol for obtaining analog screening mammograms and digital mammograms (months 1-3).
1f. Finalize advertisements for contacting participants, questionnaires, and other data collection forms (months 1-3).
1g. Order supplies for blood collection and processing, order supplies for performing assays (months 5-6).
1h. Create and finalize quality assurance audit forms to ensure safety of participants and integrity of all data (months 4-6).
1i. Update IRB protocols, informed consent documents, and HIPAA waivers for IRB submission (months 4-6).
1j. Generate standard operating procedures manual to reflect all aspects of study procedures (months 4-6).
1k. Work with Dr. Dupont to modify accrual database to include scripts and screening forms, and allow accrual and productivity reports to be generated (months 7-12).
1l. Work with the project coordinator to create REDCAP database for entry of study data (months 7-12).

Phase 2**:** Investigation Phase (Years 1 through 4)

Specific Aim 1) to assess mammographic breast density through digital mammograms; for a sample of women we will also assess mammographic breast density through analog mammograms to determine the efficacy of digital versus analog mammogram;

Specific Aim 2) to obtain information on breast cancer risk factors including health literacy, and to collect anthropometric measurements and fasting blood;

Specific Aim 3) to assay blood for select hormones and growth factors;

Specific Aim 4) to perform statistical analyses to determine the association between obesity and insulin resistance and mammographic breast density;

Specific Aim 5) to evaluate patients' ability to understand their mammogram findings as they are explained by their medical provider.

Task 2: (Drs. Sanderson, Dupont, Disher, Khoder) (Khoder replaced by Foderingham)
Quantitate mammographic breast density measurement, Months 1-42.

2a. Work with Dr. Disher to refine protocols for mammographic density analyses (months 1-12).
2b. Work with Dr. Disher to observe Cumulus computer program to quantify breast density (months 7-12).
2c. Coordinate flow of digital mammography data from the Center of Women's Health Research to Dr. Disher for quantitation (months 7-42).
2d. Assess breast density of mammograms using digital quantitative analysis to obtain the percentage of the breast occupied by breast tissue (months 7-42).

Task 3: (Drs. Sanderson, Jones, Disher) (Jones replaced by O'Hara)
Recruit subjects and collect data, Months 7-42.

3a. Screen and recruit potentially eligible women for digital mammography study at the Center for Women's Health Research (1,000 patients total) (months 7-42).
3b. Administer questionnaire (months 7-42).
3c. Perform standardized body measures; weight, height, skinfold thickness, and waist and hip circumference (months 7-42).
3d. Collect blood samples and transport to Vanderbilt molecular epidemiology laboratory for storage and processing (months 7-42).
3e. Order additional supplies as needed (months 7-42).

Task 4: (Drs. Jones, Khoder and Peterson**)** (Jones replaced by O'Hara and Khoder replaced by Foderingham) Months 7-42.

4a. Administer Short Test of Functional Literacy in Adults **(**S-TOFHLA) to study participants (months 7-42).
4b. Score S-TOFHLA instruments and categorize levels of patient's health literacy (months 7-42).

Task 5: (Drs. Sanderson, Jones, Khoder and Shu) (Jones replaced by O'Hara and Khoder replaced by Foderingham)
Process blood samples, measurements and perform stated assays, Months 7-42.

5a. Supervise research staff in acquisition and analysis of data (months 7-42).
5b. Separate serum, plasma and clot in blood sample and store at -80°C (months 7-42).
5c. Transport biospecimens to the Vanderbilt University molecular epidemiology laboratory for processing and analysis (months 7-42).

Task 6: (Drs. Khoder, Disher and Dupont) (Khoder replaced by Foderingham) Months 7-42.

6a. Obtain analog mammography films and digital mammography films for each participating patient for rating of quantitative breast density by interpretation (months 7-42).
6b. Calculate the sensitivity and specificity of each modality for detecting mammographic breast density (months 7-42).
6c. Perform statistical analyses to account for multiple comparisons in breast density subgroups (months 40-42).

Task 7: (Drs. Sanderson, Jones, Khoder **,** Dupont) (Jones replaced by O'Hara and Khoder replaced by Foderingham)

Conduct ongoing quality assurance audits to ensure patient safety and data integrity, Months 7-48. Twice monthly monitoring of activities (number of screening phone calls logged, number and type of contacts with potential or actual participants, progress with data entry, etc.).

7a. Twice monthly monitoring of study accrual (months 7-42).
7b. Continuous monitoring/reporting of potential adverse events (months 7-48).
7c. Monthly audits to verify study staff adherence to standard operating procedures (months 7-48).

Task 8: (Drs. Sanderson, Jones, Khoder, Shu, Dupont, Peterson) (Jones replaced by O'Hara and Khoder replaced by Foderingham)

Conduct interim analyses, Months 12-48.

8a. Perform interim statistical analysis (months 12-18, months 24-30, months 36-42).
8b. Preparation and submission of abstracts reflecting findings to date (months 36-48).
8c. Creation and submission of annual reports to funding agency (months 12, 24, 36).

Task 9: (Drs. Sanderson, O'Hara, Khoder, Shu, Dupont, Peterson)

Final analyses and dissemination of data, Months 22-48.

9a. Begin final statistical analyses (months 40-48).
9b. Preparation and submission of final report to funding agency (months 48).
9c. Preparation and submission of abstracts and manuscripts reflecting final results (months 40-48).

HORMONE REPLACEMENT THERAPY AND BREAST CANCER AMONG HISPANICS

M Sanderson; MS Bevel; L Alexander; AM Fair; G Peltz; H O'Hara; W Khoder
Meharry Medical College (MS, MSB, LA, HO, WK); University of Texas at Brownsville (GP); Vanderbilt University (AMF)

PURPOSE: We examined whether hormone replacement therapy was associated with breast cancer among Hispanic women living on the Texas-Mexico border.
DESIGN METHODS: We used data from a case-control study of breast cancer among Hispanics age 30 to 79 conducted between 2003 and 2008. In-person interviews were completed with 190 incident breast cancer cases ascertained through surgeons and oncologists, and 979 controls who were designated as high-risk (n=511) and low-risk (n=468) for breast cancer (with respective response rates of 97%, 83% and 74%). This analysis was restricted to postmenopausal women.
RESULTS: After adjustment for age and mammography screening, there appeared to be a borderline reduction in breast cancer risk associated with hormone replacement therapy use (odds ratio [OR] 0.69, 95% confidence interval [CI] 0.46-1.02). This reduction was more pronounced among high-risk controls (OR 0.61, 95% CI 0.40-0.94) than among low-risk controls (OR 0.76, 95% CI 0.49-1.17).
CONCLUSION: A possible explanation for the observed protective effect of hormone replacement therapy is that case women, who were presumably followed more closely than control women, may have stopped taking the therapy shortly after results from the Women's Health Initiative Trial recommended against its use in 2002. Our findings are in agreement with a recent study conducted in Arizona and New Mexico which identified a reduced risk associated with hormone replacement therapy among Hispanic women, but an increased risk among white women. Results of this study provide evidence that hormone-related breast cancer risk factors may operate differently in Hispanic women than in women of other races/ethnicities. **GRANT SUPPORT:** Research supported by grant numbers DAMD-17-03-0274 and DAMD-17-00-1-0340 from the Department of Defense, U.S. Army Medical Research and Materiel Command, and by grant number 5 P20 MD 000170 from the National Center on Minority Health and Health Disparities.

Mammographic Breast Density Study
October 18, 2013

Digital Mammograms

As of October 18, 2013, we had completed interviews with 414 participants of the proposed 480 participants of which 388 included percent breast density. Of the 26 participants missing percent breast density, 15 mammograms have not yet been read, one mammogram was not done as after the interview it was discovered the patient needed a diagnostic mammogram, three mammograms were completed but we were not able to generate percent breast density due to a technical issue, and seven mammograms were not done at the time of the interview due to a technical issue with the mammography machine and we have not been able to contact the participant to reschedule the mammogram. The approximate upper quartile (n=95) of the average percent breast density for the left and right breast combined was used to classify women as cases and the approximate lower three quartiles (n=293) was used to classify women as controls. For final analyses we will explore modeling percent breast density as a continuous variable and using restricted cubic splines.

Laboratory Assays

Originally we subcontracted with Vanderbilt Pathology Laboratory to conduct laboratory assays on fasting blood samples. Dr. Anthony Archibong from Meharry began offering these assays in January, 2013; however, he is waiting for a larger batch of samples to complete the assays. We will send him a sample of those assays completed by Vanderbilt for comparison with his assays.

Preliminary Results

The demographic characteristics and breast cancer risk factors of 95 cases and 293 controls are presented in Table 1. The mean and median anthropometric characteristics of 94 cases and 289 controls are presented in Table 2. The mean and median laboratory values of 53 cases and 183 controls completed by the Vanderbilt Lab prior to January, 2013 are presented in Table 3.

Table 1. Demographic characteristics and breast cancer risk factors of cases and controls

	Cases (n=95)		Controls (n=293)	
Characteristic	n	%	n	%
Race/ethnicity				
African American	48	50.5	169	58.3
White	20	21.0	64	22.0
Hispanic	23	24.2	42	14.5
Native American	1	1.1	1	0.3
Other	2	2.1	13	4.5
Don't know	1	1.1	1	0.4
Missing	0		3	
Spanish speaking				
No	76	80.0	257	87.7
Yes	19	20.0	36	12.3
Age (years)				
40-44	33	34.8	43	14.7
45-49	29	30.5	77	26.3
50-54	19	20.0	74	25.3
55-59	8	8.4	57	19.4
60-64	6	6.3	31	10.6
65-69	0	0.0	6	2.0
70-74	0	0.0	4	1.4
75-79	0	0.0	1	0.3
Family history of breast cancer				
No	58	65.2	195	69.2
Yes	31	34.8	86	30.5
Don't know	0	0.0	1	0.3
Missing	6		11	
Family history of diabetes				
No	35	36.8	74	25.4
Yes	55	57.9	207	71.1
Adopted	5	5.3	8	2.8
Don't know	0	0.0	2	0.7
Missing	0		2	
Age at menarche (years)				
≤12	53	55.8	143	48.8
13	17	17.9	62	21.2
>13	25	26.3	88	30.0
Menopausal status				
Premenopausal	56	59.0	90	30.7
Postmenopausal	39	41.0	203	69.3
Age at menopause (years)[a]				
<50	28	71.8	144	70.9
50-54	8	20.5	36	17.7
≥55	0	0.0	12	5.9
Don't know	3	7.7	11	5.4

Table 1. Demographic characteristics and breast cancer risk factors of cases and controls (continued)

	Cases (n=95)		Controls (n=293)	
Characteristic	n	%	n	%
Hormone replacement therapy use[a]				
No	25	64.1	147	72.8
Yes	14	35.9	55	27.2
Missing	0		1	
Number of full-term pregnancies				
0	13	13.7	23	7.9
1-2	30	31.6	83	28.5
3-4	33	34.7	124	42.6
≥5	19	20.0	61	21.0
Missing	0		2	
Age at first pregnancy (years)[b]				
<30	73	90.1	246	93.5
≥30	8	9.9	17	6.5
Missing	1		5	
Oral contraceptive use				
No	28	29.5	74	25.4
Yes	67	70.5	217	74.6
Missing	0		2	
Diabetes				
No	79	83.2	225	76.8
Yes	12	12.6	56	19.1
Borderline	4	4.2	11	3.8
Don't know	0	0.0	1	0.3
Insulin use[c]				
No	7	58.3	28	50.0
Yes	5	41.7	28	50.0
Smoking				
No	51	54.3	123	42.1
Yes	43	45.7	169	57.9
Missing	1		1	
Alcohol intake				
No	48	51.6	140	48.0
Yes	45	48.4	152	52.0
Missing	2		1	
Dietary intake				
Low	21	24.2	89	32.7
Medium	27	31.0	89	32.7
High	39	44.8	94	34.6
Missing	8		21	
Body mass index (kg/m^2)				
<25	34	36.6	28	9.7
25-29.9	28	30.1	78	27.0
30-34.9	20	21.5	80	27.7
≥35	11	11.8	103	35.6
Missing	2		4	

Table 1. Demographic characteristics and breast cancer risk factors of cases and controls (continued)

	Cases (n=95)		Controls (n=293)	
Characteristic	n	%	n	%
Physical activity				
None	23	24.2	95	32.7
Moderate	32	33.7	115	39.5
Strenuous	40	42.1	81	27.8
Missing	0		2	
Hysterectomy				
No	22	56.4	127	62.9
Yes	17	43.6	75	37.1
Previous breast biopsy				
No	79	83.2	246	84.0
Yes	16	16.8	46	15.7
Don't know	0	0.0	1	0.3
REALM health literacy				
High school	68	72.3	207	73.2
7^{th} to 8^{th} grade	22	23.4	53	18.7
4^{th} to 6^{th} grade	3	3.2	23	8.1
3^{rd} grade and below	1	1.1	0	0.0
Missing	1		10	

[a]Among postmenopausal.
[b]Among parous.
[c]Among diabetics.

Table 2. Anthropometric characteristics of cases and controls

	Cases (n=95)		Controls (n=293)	
Characteristic	Mean	SD	Mean	SD
Height (cm)[a]	161.4	6.2	161.8	7.0
Weight (kg)[b]	73.9	17.7	87.5	21.4
Body mass index (kg/m^2)[c]	28.3	6.5	33.4	7.9
Waist-hip ratio[d]	0.86	0.07	0.89	0.08
% Body fat[e]	38.1	8.3	43.7	7.5
Characteristic	Median	IQR	Median	IQR
Height (cm)	161	158-166	162	157-167
Weight (kg)	69.9	62.4-83.7	83.7	70.7-99.1
Body mass index (kg/m)^2	27.9	23.2-31.7	31.6	28.3-37.7
Waist-hip ratio	0.86	0.81-0.90	0.89	0.84-0.94
% Body fat	38.2	33.3-43.1	44.5	39.6-48.2

[a]Missing 1 case and 4 controls.
[b]Missing 2 cases and 4 controls.
[c]Missing 2 cases and 4 controls.
[d]Missing 1 case and 4 controls.
[e]Missing 3 cases and 8 controls.

Table 3. Laboratory characteristics of cases and controls

	Cases (n=53)		Controls (n=184)	
Characteristic	Mean	SD	Mean	SD
C-peptide[a]	2.5	2.0	3.1	2.0
IGF-I[b]	165.0	63.5	142.8	57.2
IGFBP3[c]	4131.5	979.6	3927.5	1112.0
Leptin[d]	22.7	16.2	35.8	25.7
Adiponectin	10.6	5.0	9.4	5.4
Characteristic	Median	IQR	Median	IQR
C-peptide	1.9	1.4-2.8	2.6	1.8-3.8
IGF-I	162	121-199	134.0	101-179
IGFBP3	4170	3460-4820	4040	3090-4600
Leptin	18.5	9.6-32.4	29.6	18.1-47.5
Adiponectin	9.0	7-14	8.0	6-11

[a]Missing 1 control.
[b]Missing 1 control.
[c]Missing 1 control.
[d]Missing 1 control.

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Perinatal factors and breast cancer risk among Hispanics

Maureen Sanderson [a,b,*], Adriana Pérez [c,d], Mirabel L. Weriwoh [a], Leah R. Alexander [a], Gerson Peltz [e], Vincent Agboto [a,b], Heather O'Hara [b], Waseem Khoder [f]

[a] *School of Graduate Studies and Research, Meharry Medical College, 1005 Dr. D.B. Todd Jr. Blvd., Nashville, TN 37208, USA*
[b] *Department of Family and Community Medicine, Meharry Medical College, 1005 Dr. D.B. Todd Jr. Blvd., Nashville, TN 37208, USA*
[c] *Division of Biostatistics, University of Texas Health Science Center at Houston School of Public Health, Austin Regional Campus, 1616 Guadalupe St., Suite 6.300, Austin, TX 78701, USA*
[d] *Michael & Susan Dell Center for Healthy Living, 1616 Guadalupe St., Suite 6.300, Austin, TX 78701, USA*
[e] *Department of Biological Sciences, University of Texas at Brownsville, 80 Fort Brown, Brownsville, TX 78520, USA*
[f] *Department of Obstetrics and Gynecology, Meharry Medical College, 1005 Dr. D.B. Todd Jr. Blvd., Nashville, TN 37208, USA*

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Breast neoplasms;
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Case–control studies

Abstract *Purpose:* This study assessed whether perinatal factors were associated with breast cancer among Hispanics, a group with fairly low incidence rates of breast cancer.

Methods: Data were used from a case–control study of breast cancer among Hispanics aged 30–79 conducted between 2003 and 2008 on the Texas–Mexico border. In-person interviews were completed with 188 incident breast cancer cases ascertained through surgeons and oncologists, and 974 controls (with respective response rates of 97% and 78%).

Results: Relative to birth weight 2500–3999 g, there was no elevation in breast cancer risk for birth weight of ⩾4000 g (odds ratio [OR] 0.76, 95% confidence interval [CI] 0.47–1.21).

Conclusions: The results tended to differ slightly from previous studies of this topic perhaps owing to the different hormonal milieu among Hispanics relative to Caucasians, African Americans and Asians in whom all previous studies of this topic

* Corresponding author at: Department of Family and Community Medicine, Meharry Medical College, 1005 Dr. D.B. Todd Jr. Blvd., Nashville, TN 37208, USA. Tel.: +1 615 321 2977; fax: +1 615 327 6296.
E-mail address: msanderson@mmc.edu (M. Sanderson).

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have been conducted. Confirmation of these findings in larger studies may assist in determining how hormonal mechanisms responsible for breast cancer differ by ethnicity.

1. Introduction

High birth weight and other perinatal factors thought to reflect on a woman's exposure to hormones, growth factors and other endocrine factors have been linked to subsequent breast cancer [1]. Three meta-analyses of the high birth weight-breast cancer association have reported summary relative risks ranging from 1.15 (95% confidence interval [CI] 1.09—1.21) to 1.24 (95% CI 1.04—1.48) [2—4], while a pooled analysis of this association based on birth records reported a pooled relative risk of 1.12 (95% 1.00—1.25) [5]. High birth weight was defined as ⩾4000 g relative to <3000 g for the most part in the meta-analyses [2—4] or relative to 3000—3499 g in the pooled analysis [5]. After restricting the types of studies to cohort studies, two meta-analyses of the association between older maternal age defined as ⩾30 years relative to <25 years and breast cancer reported summary relative risks of 1.13 (95% CI 1.02—1.25) [2] and 0.99 (95% CI 0.82—1.19) [3], respectively. Neither higher birth order (relative risk [RR] 0.91, 95% CI 0.91—1.04) nor maternal smoking (RR 0.98, 95% CI 0.86—1.13) appeared to be associated with breast cancer in a meta-analysis that included studies of all types [3]. Meta-analyses have reported breast cancer to be positively associated with birth length and older paternal age [2], negatively associated with pre-eclampsia/eclampsia and twin membership [2], and not associated with gestational age [2,3], and maternal diethylstilbestrol (DES) use [2]. However, cohort studies have identified a positive association between maternal DES and breast cancer among women diagnosed at age 40 or older [6,7]. None of the studies reported on the meta-analyses or pooled analysis examined the associations between perinatal factors and breast cancer among Hispanic women who have fairly low incidence rates of breast cancer compared with Caucasian women [8].

Based on mothers who delivered between 1974 and 1977, the birth characteristics of Hispanic women also differ from those of Caucasian women [9]. In comparison with Caucasians, Hispanics weigh slightly less (3.48 vs. 3.42 kg), are born to younger mothers (26.5 vs. 25.7 years), are of higher birth order (18.6% ⩾2 vs. 26.0% ⩾2), and are born to mothers who do not smoke during pregnancy (70.1% vs. 79.4%). Given the differences in perinatal factors and breast cancer incidence rates of Hispanics relative to Caucasians, it was assessed whether perinatal factors were associated with breast cancer among Hispanic women in the current study.

2. Materials and methods

Detailed methods of this clinic-based case—control study conducted in the Lower Rio Grande Valley located at the southern tip of Texas on the Mexico border appear elsewhere [10]. Briefly, cases of self-reported Hispanic ethnicity, aged 30—79, diagnosed with primary invasive breast cancer between November 2003 and August 2008 were identified through surgeons and oncologists shortly after diagnosis or treatment ($n = 190$, response rate 97.0%). Controls of Hispanic ethnicity, aged 30—79, were randomly selected from women receiving a diagnostic or screening mammogram at the mammography center where the case received her diagnostic mammogram. Interviews were completed with approximately five controls per case ($n = 979$, response rate 78.0%). Women who were adopted were excluded resulting in 188 cases, and 974 controls for analysis.

Written informed consent was obtained from subjects and the Institutional Review Boards of the University of Texas at Brownsville and the University of Texas Health Science Center at Houston approved this study's protocol. Trained interviewers conducted in-person interviews on demographic characteristics, suspected breast cancer risk and protective factors, medical history, physical activity, diet, body size and perinatal factors. Exposures were for a period before a reference date, the date of diagnosis for the cases and an assigned date for controls comparable to the date for the cases. For example, controls recruited early in the study were assigned reference dates ranging from November 2003 to December 2005, while controls recruited later in the study were assigned reference dates ranging from January 2006 to August 2008.

Statistical analyses were completed in SAS version 9.2. There were large percentages of missing

data for some perinatal factors (birth weight 14.2%, maternal age 13.7%, and maternal hormone use 18.1%). It was assumed that these missing values were missing at random and multiple imputation for handling these missing values were implemented. The variables listed in Tables 1 and 2 were used to perform 10 imputations under a multivariate normal model. An assumption of multiple imputation is that all variables are normally distributed which, based on a normal probability plot, was not the case for body mass index (BMI). BMI was log transformed for the imputation models and retransformed for presentation in Table 1. Logistic regression was used to estimate the relative risk of breast cancer associated with perinatal factors while controlling for potential confounding factors [11]. To assess the fit and any influential observations of the logistic regression models, Pregibon's diagnostics measures were implemented, including index plots and delta-betas [12]. Some observations were influential, but their impact on the fit was negligible. Overall, there were no concerns regarding the fitted models. Age, family history of breast cancer, age at menarche, menopausal status, parity, BMI, use of oral contraceptives, use of hormone replacement therapy, alcohol intake, number of mammograms in past 6 years, physical activity and other perinatal factors were evaluated as potential confounders. An alpha level of 0.05 was used to determine statistical significance of all two-sided statistical tests, and final analyses are presented using Rubin's rules for reporting summary statistics, odds ratios, confidence intervals, test statistics and diagnostic measures from the 10 multiple imputations [13].

3. Results

Table 1 presents the distribution of suspected breast cancer risk and protective factors by case—control status following the imputation of missing values. Cases were more likely than controls to be older, to have a family history of breast cancer, to have an earlier age at menarche, to be postmenopausal, not to have used oral contraceptives or hormone replacement therapy, to have had fewer mammograms in the past 6 years, and not to have engaged in physical activity.

The addition of age modeled continuously, menopausal status and number of mammograms in the past 6 years to the perinatal factors-breast cancer models changed the crude odds ratio by 10% or more, so adjustment was made for these confounding variables. There appeared to be no association with breast cancer among women whose birth weight was 4000 g or more relative to women whose birth weight was 2500—3999 g (odds ratio [OR] 0.76, 95% CI 0.47—1.21 after adjustment for age, menopausal status and mammography screening) (Table 2). Nor were women who were born preterm at risk of breast cancer relative to women who were born at term (OR 0.32, 95% CI 0.08—1.40). Although there did appear to be an increased risk odds of breast cancer associated with twin birth (OR 2.83, 95% CI 1.08—7.37) and maternal smoking (OR 1.44, 95% CI 0.85—2.45), the wide confidence intervals argue for cautious interpretation. There was no association with breast cancer risk odds for older maternal age or higher birth order.

4. Discussion

The results of this study, which were not statistically significant and tended to differ only slightly from previous meta-analyses [2—4] and a pooled analysis [5] of this topic, are scientifically interesting. A possible explanation for these results may be the different hormonal milieu among Hispanics relative to Caucasians, African Americans and Asians in whom all previous studies of this topic have been conducted. A recent study in the southwestern United States found that two estrogen-related factors — hormone replacement therapy and younger age at menarche — do not function as risk factors for breast cancer diagnosed after menopause among Hispanic women as they do among Caucasian women [14]. Hines et al. [14] hypothesized that the ethnic differences in postmenopausal breast cancer associated with estrogen exposure may be modified by genetic, environmental and/or lifestyle factors. They speculated this may be reflected in the higher proportion of estrogen receptor positive tumors in Caucasian women than in Hispanic women [15].

Another possible explanation for the different findings from previous studies is that *in utero* exposures may not act directly on the breast, but may alter other physiologic pathways that affect risk later in life. Terry et al. [16] investigated the cohort of daughters whose mothers participated in the New York site of the Collaborative Perinatal Project from 1959 to 1963 and found no differences in age at menarche by birth weight, maternal age, birth order, gestational age, or maternal smoking. Troisi et al. [1] indicated there is insufficient evidence to establish associations between perinatal factors and premenopausal estrogen or adult insulin-like growth factor levels, both thought to be related to breast cancer risk.

Table 1 Comparison of cases and controls for suspected breast cancer risk and protective factors.

Characteristic	Cases (n = 188)		Controls (n = 974)	
	N	%	*N*	%
Age (years)				
30–49	61	32.4	391	40.1
50–64	87	46.3	472	48.5
65–79	40	21.3	111	11.4
Breast cancer among first-degree relatives				
No	168	89.4	905	92.9
Yes	20	10.6	69	7.1
Age at menarche (years)				
<12	50	26.7	228	23.4
⩾13	138	73.3	746	76.6
Menopausal status				
Premenopausal	39	21.0	281	28.8
Postmenopausal	149	79.0	693	71.2
Full-term pregnancy				
No	10	5.3	60	6.2
Yes	178	94.7	914	93.8
Body mass index				
<25	13	7.1	69	7.1
25–29.9	44	23.6	230	23.6
30–34.9	77	41.2	401	41.2
⩾35	54	28.1	274	28.1
Oral contraceptive use				
No	66	35.3	267	27.4
Yes	122	64.7	707	72.6
Hormone replacement therapy use[a]				
No	90	60.3	431	44.3
Yes	59	39.7	543	55.7
Alcohol intake				
No	154	81.9	798	81.9
Yes	34	18.1	176	18.1
Number of mammograms in past 6 years				
0–1	39	20.7	97	10.0
2–3	54	28.7	187	19.2
4–5	34	18.1	186	19.1
⩾6	61	32.4	504	51.7
Physical activity				
No	115	61.2	485	49.8
Yes	73	38.8	489	50.2

[a] Among postmenopausal women.

Lastly, these results may have been explained by insufficient study power. This study power was limited for all main effects; in order to achieve 80% power for the high birth weight-breast cancer association, this study would have required 725 cases and 2900 controls.

This study was limited by self-report of perinatal factors which is prone to misclassification and resulted in many missing values. Several validation studies of perinatal factors have been performed, including one that was conducted on women born in Washington State in which very high correlations comparing self-report with birth certificate for maternal age (r = 0.95), and comparing self-report with mother report for birth order (r = 0.89) and for birth weight (r = 0.85) [17] were found.

Table 2 Odds ratios of breast cancer associated with perinatal factors.

Characteristic	Cases (n = 188)		Controls (n = 974)		OR[a]	(95% CI)
	N	%	N	%		
Birth weight (g)						
<2500	28	15.1	164	16.8	0.76	(0.47—1.21)
2500—3999	146	77.3	708	72.7	1.00	(Referent)
⩾4000	14	7.6	102	10.6	0.68	(0.36—1.29)
Maternal age (years)						
<25	84	44.8	392	40.2	1.00	(Referent)
25—29	42	22.3	226	23.2	0.92	(0.58—1.46)
⩾30	62	32.9	356	36.6	0.84	(0.57—1.25)
Birth order						
First	40	21.1	205	21.0	1.00	(Referent)
⩾Second	148	78.9	769	79.0	1.00	(0.95—1.05)
Gestational age (weeks)						
<37	2	1.3	27	2.8	0.32	(0.08—1.40)
⩾37	186	98.7	947	97.2	1.00	(Referent)
Twin birth						
No	180	95.7	962	98.8	1.00	(Referent)
Yes	8	4.3	12	1.2	2.83	(1.08—7.37)
Maternal smoking						
No	164	87.3	893	91.7	1.00	(Referent)
Yes	24	12.7	81	8.3	1.44	(0.85—2.45)

[a] Odds ratio (OR) and 95% confidence interval (95% CI) adjusted for age, menopausal status and number of mammograms in past 6 years.

The percentage of women unable to report some of their perinatal factors ranged from 1.6% for birth order to 18.1% for maternal hormone use. With the exception of gestational age, cases were slightly more likely than controls to have missing values. Although the percentages of missing values tended to be similar for cases and controls, it was not clear as to whether the missing value would have been systematically lower or higher than the obtained value, thus multiple imputations may have resulted in a differential misclassification. Differential misclassification may have biased results toward or away from the null, but in comparing multiple imputations with other methods for analyzing data with large percentages of missing values, multiple imputation produces less biased and more efficient estimates [18]. Additional limitations were the inability to calculate an odds ratio for maternal hormone use because no mothers of cases reported hormone use, and this study's failure to collect information on birth length, paternal age and pre-eclampsia/eclampsia which were associated with breast cancer in a meta-analysis [2]. In addition, this study was unable to assess effect modification by menopausal status owing to the small number of premenopausal cases (n = 39), which is of importance since Sanderson et al. [19] identified differing birth weight-breast cancer associations for premenopausal and postmenopausal women.

As far as this study is concerned, it is the first to investigate the association between perinatal factors and breast cancer among Hispanic women. Given the differing distributions of perinatal factors in Hispanic women relative to women of other ethnicities, it is important to include this group to further clarify the contribution of prenatal exposures to adult-onset diseases. This study was unable to categorize birth weight differently because 35% of women who were unable to report their exact birth weight reported it as less than 2500, 2500—3999 or 4000 g or more. However, a sensitivity analysis was performed comparing women who were first born with those who were second born (OR 1.03, 95% CI 0.61—1.75), third born (OR 0.99, 95% CI 0.56—1.74) and fourth born or higher (OR 0.91, 95% CI 0.59—1.38) which revealed a reduction in risk with higher birth order. Lastly, this study assessed confounding by a number of established breast cancer risk and protective factors, including mammography screening, which reduced the likelihood of detection bias.

Hispanic women have relatively low incidence rates of breast cancer although they possess some of the same risk factors as ethnic groups with higher incidence rates. As Hines et al. [14] suggest, the study of Hispanic women may help us disentangle the effect of the hormonal milieu on breast cancer. Confirmation of these findings in larger studies may assist in determining how hormonal mechanisms responsible for breast cancer differ by ethnicity.

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